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2

Definitions

Collecting the evidence needed to develop effective diagnostic approaches, prevention strategies, therapies, and management procedures to prevent, manage, and treat food allergy requires that the physicians, biomedical and pharmaceutical scientists, policy makers, affected individuals and families, and all other stakeholders share a common understanding of what food allergy is and is not. In addition, although all proteins in foods have the potential to elicit a food allergy, some have been recognized as major allergens due to their potency in inducing a food allergy or in affecting the prevalence of allergy to those food constituents in the population. The list varies depending on the country but several ones are common globally. This introductory chapter begins by defining food allergy both by describing its signs and symptoms and by presenting our current understanding of how food allergy develops in affected individuals. The chapter also distinguishes food allergy from the many other adverse effects or conditions that could be related to foods but that have a nonimmunological origin. Considering the diversity of food adverse conditions with similar symptomatology and clinical manifestations (see Figure 2-1), it is no wonder that many misconceptions persist about food allergy. Even today, many questions are still unresolved. The most pressing research questions are detailed in Chapter 9.
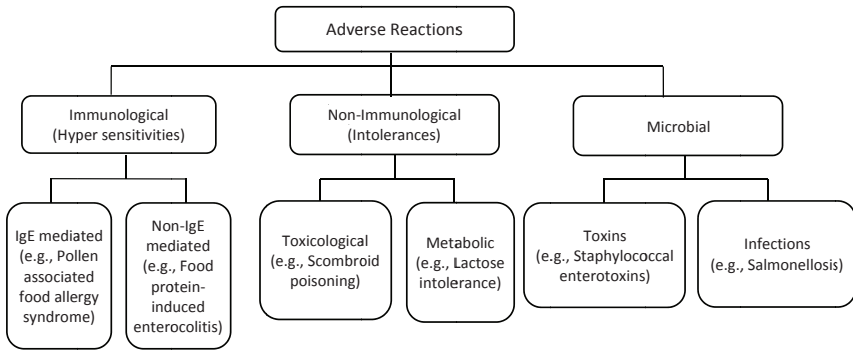
FIGURE 2-1 Types of adverse reactions to foods.

FOOD ALLERGIES: DEFINITIONS

Commonly Accepted Definitions

Food allergy is "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food," according to the 2010 National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIAID/NIH)-supported *Guidelines for the Diagnosis and Management of Food Allergy in the United States* (NIAID/NIH-supported Guidelines) (Boyce et al., 2010). "Exposure" in the food allergy context can be through ingestion, skin contact, or exposure to airborne particles. The immunologic component is central to the discussion of food allergy, including the underlying mechanisms of allergic reactions and methods of diagnosis and treatment. Adverse reactions to foods or food components that lack an identified immunologic pathophysiology are not considered food allergy, but instead are typically called food intolerances (Boyce et al., 2010). These reactions are not a focus of this report. The mechanisms behind these other conditions may include metabolic, pharmacologic, or toxic factors.

A food is defined as "any substance—whether processed, semi-processed, or raw—that is intended for human consumption, and includes drinks, chewing gum, food additives, and dietary supplements" (Boyce et al., 2010). Food allergens are the components within foods that trigger immunologic reactions. These are most often specific glycoproteins, which can interact with the body's immune cells in a way that initiates the development of a food allergy.

The broad terms **allergy** and **allergic disease** refer to a disease caused by immunologic dysfunction that fall under one of two key classifications: immunoglobulin E (IgE)-mediated or non-IgE-mediated (see Tables 2-1 and 2-2). This report focuses almost exclusively on IgE-mediated food allergy, which has better defined underlying cellular mechanisms and an established link to many prevalent food allergy reactions. Non-IgE-mediated food allergy reactions (e.g., food protein–induced enterocolitis) are less common and the mechanisms of the reactions are less well characterized. Celiac disease is a well-characterized, immune-mediated disease that has food as an exacerbating factor but will not be detailed in this report.

Immunoglobulin E is an antibody that, if bound to certain cells bearing receptors for IgE, can trigger intense inflammatory reactions in response to the allergen for which the cell-bound IgE has specificity. The presence and quantity of such allergen-specific IgE antibodies is a key metric in diagnosing and evaluating food allergy sensitivities. However, the quantity of IgE antibodies ranges widely, making quantification an incomplete

TABLE 2-1 Overall Differences Between IgE- and Non-IgE-Mediated Food Allergies

Class	IgE-Mediated	Non-IgE-Mediated
Time to onset of reaction	Immediate <2 hours[a]	Delayed Often >4-6 hours
Volume usually required for reaction	Small	Sometimes larger
Typical symptoms	Urticaria Angioedema Vomiting Diarrhea Oral itching Anaphylaxis	Diarrhea Food refusal Failure to thrive Gastroesophageal reflux Irritability/abdominal distension Eczema
Common diagnostic procedures	Above signs or symptoms by history or oral food challenge and positive IgE antibody (skin prick test or serum specific IgE)	Sometimes can do home-based elimination and rechallenge sequence; some require rechallenge in hospital setting

[a] In the case of mammalian meat, onset times for reactions related to galactose-alpha-1, 3-galactose (alpha-gal) can be longer than 2 hours. (See "Delayed Anaphylaxis Associated with Mammalian Meats" in Chapter 4.)

TABLE 2-2 Types of Food Allergies

GI Food Allergies	
IgE-mediated	
Immediate gastrointestinal (GI) hypersensitivity	Upper GI symptoms may occur within minutes; lower GI symptoms may occur either immediately or with a delay of up to several hours. Immediate vomiting is the most common reaction and the one most clearly mediated by IgE.
Pollen-associated food allergy syndrome (PFAS)	PFAS is an IgE-mediated allergy, often to raw fruits or vegetables, with symptoms including itching or swelling of the lips, mouth, and throat.
Non-IgE-mediated	
Eosinophilic gastroenteritis (EG)	EG is thought to be non-IgE-mediated although IgE-mediated is possible. EG symptoms vary depending on the portion of the GI tract involved and the localized or widespread infiltration of the GI tract by eosinophils.
Eosinophilic esophagitis (EoE)	EoE symptoms vary depending on the age of the person, from reflux-like symptoms and vomiting in school-age children, to refusal to eat and impaction in teenagers and adults.
Food protein–induced enteropathy	Vomiting, diarrhea, and sometimes protein-losing enteropathy occur in this condition.
Food protein–induced allergic proctocolitis (AP)	AP typically presents as specks or streaks of blood mixed with mucus in the stool of otherwise healthy infants. Food-specific IgE is generally absent. The suspected role of food allergy is based on history of exposure to allergens, not diagnostic tests.
Food protein–induced enterocolitis syndrome (FPIES)	Non-IgE-mediated FPIES usually occurs in infants and presents as chronic emesis, diarrhea, and failure to thrive. Milk and soy protein are the leading, but not exclusive, causes. The reaction is delayed, occurring approximately 2 hours or later after ingesting the food.
Cutaneous	
IgE-mediated	
Acute urticaria	Round and irregular pruritic (itchy) lesions appear quickly after ingesting an allergenic food. Although IgE-mediated food allergy often causes urticaria, it is not the leading cause.
Angioedema	Likely IgE-mediated when caused by food and involves "non-pitting, non-pruritic, well-defined edematous swelling that involves subcutaneous tissues, abdominal organs, or the upper airway." Upper airway involvement signifies a likely medical emergency.

TABLE 2-2 Continued

Contact urticaria	Can be induced by either an IgE-mediated food allergy or a nonimmunologic histamine reaction.
Non-IgE-mediated	
Atopic dermatitis (AD)	AD involves complex interactions between skin barrier dysfunction and environmental factors, linked in some individuals to mutations in the protein filaggrin. The role of food allergy, from sensitization to subsequent skin reaction, remains a topic of debate.
Allergic contact dermatitis (ACD)	ACD is a form of eczema caused by reactions to chemical haptens in foods; it is associated with marked pruritus, erythema (redness of the skin), papules, vesicles, and edema.

SOURCE: Boyce et al., 2010.

indicator of function, allergen sensitivity, or reaction severity. Moreover, some individuals with measurable IgE specific for particular food allergens do not exhibit clinical signs and symptoms of food allergy when they ingest such allergens. This supports the conclusion that allergen-specific IgE is (by definition) required for a person to exhibit clinical food allergy to that allergen, but the presence of such allergen-specific IgE is not sufficient for a person to exhibit a food allergy to that allergen. IgE is typically measured in serum or determined through allergen skin prick tests (Berin, 2015). The IgE-mediated reactions observed in patients with food allergy are often grouped into immediate onset reactions and immediate plus late-phase reactions and can include life-threatening anaphylaxis, gastrointestinal hypersensitivity, urticaria, and pollen-associated food allergy syndrome (Berin, 2015). Allergen-specific IgE may be detectable in atopic dermatitis (AD) and eosinophilic esophagitis (EoE) and these may be food-responsive disorders, but a direct correlation of the pathology in these disorders with IgE and specific food allergen triggers is less clear (see Box 2-1 for these and other basic definitions).

Common Food Allergy Signs and Symptoms

Food allergy can manifest through a wide range of signs and symptoms with varying severity, which makes diagnosis challenging, particularly if a history of allergic reactions has not already been established (see Chapter 4). The most common signs and symptoms typically manifest on the skin (i.e., cutaneous), in the gastrointestinal (GI) tract, in the respiratory system, or in all of these areas. These signs and symptoms include development of uticaria (hives), angioedema (tissue swelling), circulatory collapse, dizziness, coughing, vomiting, stomach cramps, nausea, and others (ACAAI, 2015).

BOX 2-1
Definitions

Allergen-specific IgE is an IgE that recognizes a specific allergen and that is formed by the immune systems of some individuals after they have been exposed to that allergen in food.

Anaphylaxis is an acute, potentially life-threatening syndrome with multisystemic manifestations due to the rapid release of inflammatory mediators.

Desensitization is a state of clinical and immunological nonresponsiveness to an allergen, including food allergens, that can be induced by the careful, physician-guided administration of gradually increasing amounts of the offending allergen over a relatively short period of time (hours to days). The maintenance of such desensitization typically requires continued regular exposure to the offending allergen (also see **Tolerance**).

Food allergens are the components within foods that trigger adverse immunologic reactions; these are most often specific glycoproteins that can interact with the body's immune cells in a way that initiates the development of a food allergy.

Food allergy is an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food, and that can be either IgE-mediated or non-IgE-mediated.

Food intolerance is an adverse reaction to foods or food components that lacks an identified immunologic pathophysiology.

Food allergy is rarely the principal cause of respiratory conditions, but IgE-mediated respiratory symptoms can be a key finding in diagnosing anaphylaxis (James, 2003). In addition, occupational asthma caused by exposure to food occurs more frequently among individuals in certain professions such as bakers, millers, or grain elevator workers. A number of specific cutaneous and GI food allergy conditions, as defined by the NIAID, are listed in Table 2-2. Food-induced anaphylaxis—which may accompany or encompass other conditions—is an acute, potentially life-threatening syndrome with multisystemic manifestations due to the rapid release of inflammatory mediators (Boyce et al., 2010). It can occur within minutes to a couple of hours of ingesting the food (or longer for alpha-gal reactions related to mammalian meat). The reaction usually develops and, if appropriately treated, resolves completely within hours, but in rare

Immunoglobulin E (IgE) is a type of antibody that can trigger intense inflammatory reactions. IgE causes the IgE-mediated allergic response by binding strongly to IgE receptors (FcεRI) found on the surface of mast cells and basophils, and triggering these cells to release powerful inflammatory mediators once the cell-bound IgE recognizes the offending food allergen.

Pollen-associated food allergy syndrome (PFAS) is a type of food allergy with signs and symptoms that include itching or swelling of the lips, mouth, or throat in response to eating certain raw fruits and vegetables. PFAS typically develops in adults with hay fever. The specific IgE antibodies formed exhibit reactivity with both proteins found in pollen and similar proteins found in certain fruits and vegetables.

Sensitization is a condition in which an individual produces detectable IgE to a particular allergen or allergens. It precedes and is required for the clinical manifestations of a food allergy, but not all individuals with detectable IgE will experience a food allergy reaction to the allergen recognized by that IgE.

Tolerance is a state of unresponsiveness of the immune system to substances or tissue that have the capacity to elicit an immune response. It can be natural (e.g., to the body's own proteins) or acquired (e.g., to external proteins). It is also said that some persons can "grow out" of an allergy; this can be envisioned as a form of acquired tolerance to the offending allergen(s). In some instances, the state of tolerance may be transient (also see **Desensitization**) and in others it can be durable.

instances symptoms can occur hours later. For some individuals, exercise after ingesting an allergenic food may increase the likelihood of anaphylaxis and severity of clinical symptoms (Romano et al., 2001). In those with severe and potentially life-threatening anaphylaxis, findings include airway compromise (swelling of tissues in the throat and upper airways), impaired breathing (e.g., nasal congestion and rhinorrhea and narrowing of airways in the lungs), and/or circulatory problems (e.g., changes in heart rate, shock). Skin and mucosal changes usually, but not always, also occur (e.g., flushing, pruritus, hives in the skin; swelling of the tissues of the lips, mouth, and GI system). For a more detailed description of anaphylaxis and its diagnosis and management, see Chapter 6.

Common Allergenic Foods and Food Allergens

Although, in theory, any protein molecule could be allergenic and a large number of foods have been noted to cause IgE-mediated food allergy, a small number of foods cause most of the clinical reactions (Boyce et al., 2010). Foods that are categorized as allergenic differ by country because the prevalence of food allergy caused by various foods differs by region of the world and according to the eating habits within a population. In the United States, the foods listed below are currently considered allergenic for regulatory purposes. However, the committee did not restrict its findings, conclusions, and recommendations to this list, and has included foods that are viewed as allergenic by other countries (e.g., sesame and some fruits and vegetables). The lists have regulatory implications for managing allergens (e.g., food product labeling) that affect many stakeholders. Importantly, the foods that are or are not on these "official" lists of allergens affect consumers who need to avoid specific allergens, both in their country and when they travel internationally. Chapter 7 includes a description of the criteria that different countries follow in order to categorize a food as allergenic and a list of foods that are commonly considered allergenic in various countries. Chapter 7 also includes the committee's recommendations to update the list of allergens in the United States.

In each of these allergenic foods, specific glycoproteins trigger the reaction and production of IgE antibodies that are reactive with those glycoproteins (during the period when the patient is becoming sensitized to those allergens). Clinical reactions are then triggered upon re-exposure to such foods after sensitization has occurred. Identifying and tracking these allergenic proteins and how they are affected by factors such as variation in food preparation is crucial to understanding mechanisms of food allergy reactions and potential avenues of prevention or treatment. For example, it will be important to understand how and why certain processes of food preparation can neutralize or diminish the ability of allergens either to induce sensitization or elicit clinical reactions (see also Chapter 7). Each type of allergenic food can contain a major or several allergenic proteins, as illustrated by the following list:

- **Peanuts:** Ara h 1, Ara h 2, Ara h 3, Ara h 8, Ara h 9
- **Milk:** aS_1-casein, aS_2-casein, β-casein, κ-casein, β-lactoglobulin, α-lactalbumin
- **Eggs:** ovomucoid, ovalbumin, ovotransferrin, lysozyme
- **Fish:** parvalbumin
- **Shellfish:** tropomyosin
- **Wheat:** Tri a 12, Tri a 14, Tri a 19, Tri a 21, Tri a 26
- **Soy:** Gly m 1, Gly m 4, Gly m 5, Gly m 6, Gly m 8

Food Allergy Misconceptions

Perceptions of food allergy conditions, patterns, and treatments can have a profound impact on both patient safety and cultural/societal accommodations for those with food allergy. Misconceptions persist among doctors, patients with allergies, and the general public—some of which could be potentially dangerous. Misconceptions are particularly significant among parents or guardians, as food allergy often manifests first in children.

Misconceptions fall into two major types: those related to basic concepts or management of a food allergy. This section addresses the former. The timing of the clinical symptoms after food ingestion, how long symptoms of food allergy actually last after ingestion, and the foods more or less likely to cause severe symptoms are often misunderstood. Bock (1987) reported that 28 percent of parents thought that their children had adverse reactions to foods but only 8 percent of the children actually did when challenged with the food. The Chicago Food Allergy Research Survey for Parents of Children with Food Allergy, a study conducted in 2008, solicited answers from 2,945 parents from across the United States (Gupta et al., 2010a); significant misconceptions or absences in knowledge were revealed. Some 52 percent of parents answered that anaphylaxis was more likely to be fatal in children than in adolescents, while the opposite is true. Almost half of participants believed that there is a cure for food allergy and more than two-thirds believed that a medicine could be taken as prevention. Furthermore, 40 percent of respondents reported "experiencing hostility from other parents when trying to accommodate their child's food allergy." That perceived hostility might point to a lack of awareness among the general public, which can fail to recognize legitimate food allergy dangers. However, another study (Gupta et al., 2009) concluded that most members of the public recognize the real risk of food allergy–related deaths and can even identify key symptoms. Other misconceptions among surveyed parents include a belief that food additive allergies are common (actually rare, despite the prevalence of additives in processed foods) and a lack of awareness about the rates at which children outgrow certain food allergy sensitivities (Gupta et al., 2010a).

These inaccurate beliefs were less common among parents who visited allergists rather than primary care physicians, which points to the potential lack of knowledge outside of specialists. Medical practitioners, and especially allergists, have an ongoing responsibility to educate the public, patients, and their fellow physicians (see Chapter 6). However, numerous studies suggest deficits in understanding these basic concepts among many different stakeholders, including physicians (Desjardins et al., 2013; Morawetz et al., 2014). Various surveys indicate misunderstandings among medical professionals in recognizing risk factors for food allergy reactions,

including anaphylaxis (Clark et al., 2004; Gupta et al., 2010b; Turner et al., 2016; Wang et al., 2014).

Knowledge deficits regarding food allergy also have been noted among school nurses (Carlisle et al., 2010), child care providers (Greiwe et al., 2015), emergency response providers (Jacobsen et al., 2012), restaurant personnel (Ahuja and Sicherer, 2007; Bailey et al., 2011), and teachers (Ercan et al., 2012; Polloni et al., 2013). Overall, stakeholders and the general public are currently insufficiently educated (see also Chapters 4, 5, and 6).

MECHANISMS

Mechanisms of Disease

This report is not meant to delve deeply into the basic mechanisms underlying food allergy, but mainly to address more practical aspects, such as diagnosis and management. Still, unraveling the pathological processes of food allergy is critical for understanding how to diagnose and clinically evaluate food allergy and for developing short- and long-term mitigation strategies. The intricate biological systems involved and the wide range of clinical manifestations of food allergy make this a long-term process characterized by incremental, albeit ultimately important, progress. For purposes of this report, this section briefly explores two principal aspects of clinical food allergy: the mechanism of the reaction and the mechanism of immunological tolerance. Figure 2-2 represents the mechanistic interactions and complexities of food allergy, which are not fully described in this section. For a more detailed description of the processes readers are referred to other publications (e.g., Berin, 2015; Chinthrajah et al., 2016).

Specific food allergies likely are a result of complex interactions among genes and the environment (including not only factors in the "external environment," such as pollen, pollution, and pathogenic microbes, but also effects of the microbes that normally reside in us—the "internal environment" of the microbiome) (see Chapter 5 for a detailed description of current knowledge on food allergy determinant factors).

With IgE-mediated food allergy—the classification under review here—allergic sensitization must precede manifestation of the full reaction. Sensitization is defined as the process by which an individual produces detectable IgE to a particular allergen (allergen-specific IgE [sIgE]). This can be called, operationally, the "offending allergen." (See also Figure 2-2 for an explanation of this process and Box 2-2 for definitions of key cellular components in food allergy reactions.) However, it is important to recognize that sensitization alone does not constitute clinical food allergy. In fact, sensitization can persist without the patient manifesting any clinical signs of food allergy.

This finding is an important part of understanding the diagnostic workup in food allergy. Having sIgE against a food allergen means the person has been sensitized to that allergen and therefore might exhibit a clinical food allergy reaction to that allergen, but a more specific test (the double-blind, placebo-controlled oral food challenge) would be required to diagnosis an allergy to that food in such a sensitized person.

Some allergens produce organ-specific reactions, but the mechanisms that could explain such clinical variation are not well understood. For example, peanut and egg are the most common triggers of GI symptoms, and peanut causes more respiratory reactions than other allergens (Berin, 2015).

It has been increasingly recognized that skin exposure can be a powerful driving factor in food sensitization. One leading hypothesis about how sensitization occurs is that humans naturally become tolerant to food encountered orally in the diet, but sensitization is favored, at least in "susceptible" individuals, through skin exposure (see Chapter 5). The interplay between reactions occurring in the skin and within the GI tract is thought to be an important element of sensitization. For example, loss-of-function variants in the gene encoding filaggrin, a key protein in the regulation of epidermal barrier function and health, have an established link to eczema, but research also links variants in filaggrin to food allergy (Lack, 2012). Lack of normal skin barrier integrity facilitates the development of food allergy. Peanut sensitization in particular is linked with skin exposure, but studies also show that childhood use of lotions containing oat led to much higher rates of oat allergies (Boussault et al., 2007). The molecular underpinnings of this hypothesis, however, are not fully understood.

Mechanisms of Tolerance and Desensitization

Two major terms that are used for defining a situation that is commonly known as "growing out" of a food allergy are desensitization and tolerance (see Figure 2-1). In some instances, natural tolerance (as opposed to the tolerance induced by specific therapeutic interventions) to some foods that once induced food allergy in that individual will develop over time. Accounts of spontaneous resolution of IgE-mediated food allergy vary according to food, age, and geography, but estimates indicate that 65 to 80 percent of individuals will develop such natural tolerance for cow milk, wheat, soy, and egg, and only 10 to 20 percent for peanut and tree nuts (Campbell et al., 2015).

For those who have not acquired tolerance naturally, a cure for food allergy does not exist yet. Strategies of management and treatment include avoidance of allergens, immediate treatment of symptoms, and the induction of tolerance. Multiple mechanisms play a role in regulating food allergy, many of which are extrathymic, resulting in a range of clinical

FIGURE 2-2 Mechanisms by which a person first becomes sensitized to a food allergen and subsequently can develop an acute allergic reaction when exposed again to that food allergen.

A. Sensitization is the process by which food allergens induce the development of food-specific serum IgE (sIgE). **1A.** Allergens present in foods cross the small intestinal epithelium (if present in the individual's environment; for example, peanut proteins also may enter the body through the epidermis of the skin [not shown]). These processes can be enhanced at sites that have genetically-determined or acquired defects in normal barrier function, such as at sites in the skin affected by atopic dermatitis (also known as eczema). **1B.** This initial exposure to allergen does not elicit an acute reaction, such as in the intestines, because there is no allergen-specific IgE present at this time. However, **(2)** the allergen is taken up and processed by a dendritic cell (DC) located in the intestinal mucosa (or skin [not shown]) which then **(3)** migrates to a regional lymph node (or to another location in the intestinal mucosa or skin). **4.** The DC presents the processed allergen-derived peptide to a naïve T cell whose T cell receptor is specific for that allergen-derived peptide. The DC does this by presenting the allergen-derived peptide (that is physically associated with a major histocompatibility complex (MHC) class II molecule on the DC membrane) to the T cell by way of the T cell's membrane-associated T cell receptor (TCR). The DC and naïve T cell also are bound to each other by co-stimulatory molecules (e.g., jagged on the DC membrane and notch on the T cell membrane) that enhance this cell-cell interaction. **5.** In the presence of IL-4 (that can be derived from any of a number of cell sources) such naïve T cells acquire features of a T helper cell type 2 (Th2 cell, a type of T cell that can help to drive the sIgE production seen in patients who become sensitized to allergens) and this T cell clone expands by proliferation. **6.** A Th2 cell bearing the TCR that recognizes the specific allergen-derived peptide interacts with a B cell whose B cell receptor has recognized some component of the same allergen (that may have entered the environment of the B cells located in lymphoid tissue by travelling through lymph draining the tissues of the intestines or skin) and has internalized and processed it into an allergen-derived peptide that it presents to the allergen-derived peptide-specific Th2 cell by way of the MHC class II molecule on the B cell surface. The Th2 cell and B cell also interact physically through co-stimulatory molecules (shown are Th2 cell ICOS and CD40 ligand interacting with B cell ICOS ligand and CD40, respectively). This Th2 cell-B cell interaction activates both cells (e.g., the Th2 cells increase production of IL-4 and IL-13, which, along with the CD40-CD40 ligand interaction, stimulates the B cells to switch to production of sIgE) and to differentiate into plasma cells that **(7)** can produce and secrete large amounts of the sIgE, which can diffuse locally in the tissues and enter the blood, resulting in the systemic distribution of sIgE to other sites in the body. **8 & 9.** The sIgE is bound with high affinity (i.e., strongly) to special receptors for IgE (FcεRI) that are present in large numbers on the surface of **(8)** mast cells, that are located in the tissues of the gastrointestinal tract and (not shown) the skin, upper and lower airways, and many other anatomic sites, and **(9)** basophils, leukocytes that are present in low numbers in the circulating blood. Because mast cells and basophils have thousands of FcεRI on their surface, they can bind many IgE antibodies, including those specific for this allergen (sIgE, shown in green in the figure) and those with specificities for other allergens or non-allergens (shown in blue in the figure). The presence of these sIgE molecules on the surface of mast cells and basophils gives little or no activation signal to the cells, but prepares them to undergo activation upon subsequent exposure to the allergen recognized by the sIgE.

FIGURE 2-2 Continued

B. Immediate GI Hypersensitivity. This is the rapidly developing reaction ob-
served when some sensitized subjects are exposed to allergen recognized by their
sIgE. It is important to emphasize that, for reasons not understood, many sensi-
tized subjects do not develop any clinical reactions upon exposure to the allergens
recognized by their sIgE whereas other sensitized individuals can rapidly develop
severe reactions upon exposure to the same allergen. **1A.** The sensitized individual
consumes a food containing the allergen recognized by that person's sIgE, and the
allergen passes through the intestinal epithelium, initiating a series of processes
that can (**1B**) rapidly (within minutes for many common food allergens, but within
hours for certain allergens present in red meats) induce a clinical response, including
contraction of the smooth muscle of the intestines. **2.** The allergen, now in the in-
testinal tissues, is recognized by two or more sIgE molecules bound to FcεRI on the
surface of a mast cell, causing aggregation of the sIgE and the FcεRIs to which they
are bound, thereby activating the mast cell to release histamine and a wide variety
of other chemicals ("mediators," such as prostaglandin D_2 [PGD_2], cysteinyl leu-
kotrienes [cys-LTs], leukotriene B_4 [LTB_4], and platelet activating factor [PAF]) and
cytokines (such as tumor necrosis factor [TNF], interleukin 8 [IL-8], monocyte che-
moattractant protein-1 [MCP-1], and vascular endothelial growth factor [VEGF])
that can have diverse effects on the local cells and tissues, and, when released in
large quantities, can enter the blood and cause signs and symptoms in other sites
like the skin, upper and lower airways, and cardiovascular system. Effects of the
released mast cell mediators and cytokines include (**3**) increased intestinal peristalsis
and contractions, (**4**) stimulation of local nerves to release neuropeptides, which (**5**)
can induce effects on intestinal smooth muscle and (**6**) together with products de-
rived from activated mast cells, can increase mucus production by epithelial goblet
cells, (**7**) vasodilatation of blood vessels, (**8**) increased permeability of certain blood
vessels, resulting in the leakage of fluid into the tissues, which (**9**) favors the entry
of allergens from the tissues into the blood stream. Once allergen has entered the
blood, it can (**10**) bind to sIgE on the surface of blood basophils, causing aggrega-
tion of their FcεRIs, thereby activating the basophils to release biologically active
mediators and cytokines that partially overlap with those secreted in the tissues by
mast cells. Products of activated mast cells also can (**11**) induce local structural cells,
such as intestinal epithelial cells, to (**12**) release products that can in turn influence
mast cell functions, including enhancing their secretion of mediators (**11**). Along
with (**13**) products secreted by activated mast cells, such products derived from
epithelial cells can have effects on local blood vessels that favor the local develop-
ment of inflammation, such as (**14**) the recruitment of circulating leukocytes. These
recruited leukocytes can help perpetuate the local inflammation, resulting in "late
phase reactions" (LPRs) that are associated with clinical signs and symptoms that
may persist or recur even hours after the initial exposure to the offending allergen,
and that may need continued treatment.

BOX 2-2
Definition of Key Cellular Components
in Food Allergy Reactions

Basophils (basophilic granulocytes), the least abundant of the granulocytes (the others being neutrophils and eosinophils), can release histamine, lipid mediators, and cytokines in response to the aggregation of their cell surface FcεRI, which is induced when IgE bound to these FcεRI recognizes specific allergens, including those from foods. Unlike mast cells, basophils mature in the bone marrow and circulate in the blood, but can enter tissues at sites of allergic inflammation.

Cytokines are small proteins produced by various immune cells and other cell types that carry signals to facilitate communication and interaction between cells.

Epitopes are the specific fragments of food allergens (antigens) that the immune system recognizes; if recognized by IgE bound to FcεRI on the surface of mast cells and basophils, epitopes can trigger an allergic reaction that may include anaphylaxis.

FcεRI is the high-affinity receptor for IgE that binds IgE and thereby permits cells bearing FcεRI on their surface (e.g., mast cells, basophils, some dendritic cells, and macrophages) to become "sensitized" so that they then can be activated to release inflammatory mediators by allergens recognized by the bound IgE. For the FcεRI to initiate the cell signaling that results in activation of mast cells and basophils to release their mediators requires that the receptors are aggregated when their bound IgE reacts with allergens that are at least bivalent (e.g., have two epitopes that can bind IgE). This permits such allergens to bridge adjacent IgE molecules and to aggregate the FcεRI receptors that bind such IgE.

Mast cells are derived from hematopoietic precursors that mature after migrating into essentially all vascularized tissues, where they can reside for long periods of time. Mast cells are present within the mucosal tissues of the entire GI tract (and many other anatomical sites, including the skin and airways) and contain cytoplasmic granules rich in histamine, proteoglycans (depending on the mast cell population, these consist of heparin and/or chondroitin sulfates), serine proteases (depending on the mast cell population, these can consist of carboxypeptidase A3, tryptases, and/or chymase). Upon activation by IgE and specific antigens (including food allergens), mast cells can release such granule-associated inflammatory mediators and also secrete newly synthesized lipid mediators and cytokines. Mast cells also can be activated by diverse agents that act independently of IgE, which can result in the release of the same products produced by mast cells activated through IgE.

T cells are lymphocytes produced by the thymus that guide many aspects of the immune system, particularly its adaptability and ability to recognize threats.

recommendations and conflicting data (Campbell et al., 2015). Hallmarks of tolerance include a reduction in sIgE production, decreased allergen-IgE-induced basophil activation, increased allergen-specific IgG4, and induction of T regulatory (Treg) cells (Berin, 2015; Campbell et al., 2015; Chinthrajah et al., 2016).

Recent studies have begun to investigate specific treatments to induce food allergy desensitization or tolerance. It is important to understand that the term desensitization is used here to mean that, while continuing on a specific course of treatment with the offending allergen, the individual will tolerate more of the food on food challenge, even in some cases to the point of not reacting to "serving sized" amounts of the food. Desensitization, however, does not guarantee true tolerance (defined here as a long-term loss of clinical reactivity to the allergen under conditions of no further exposure to the offending allergen). A more recent term, "sustained unresponsiveness" was coined to describe what happens when the treatment for food allergy is stopped. In some such individuals, unresponsiveness to the offending allergen lasts weeks to months, while in others, desensitization is lost more quickly. The mechanisms that may explain desensitization versus sustained unresponsiveness versus true tolerance are being intensely investigated, as are approaches of immune system monitoring that might help classify individuals into one of these three groups with respect to the outcome of treatment. Some of the mechanisms by which treatments for food allergy may be associated with changes in the clinical symptoms include the occurrence during the treatment of natural tolerance noted above (this is one reason why clinical studies of new treatments would include a placebo group), reduction in production of allergen-specific IgE, decreased antigen- and food-specific IgE-dependent basophil activation, increased allergen-specific IgG4 (one effect of which may be to bind allergen before it can be encountered by sIgE and the surface of basophils and mast cells), and the induction of Treg cells or anergic T cells (Campbell et al., 2015). However, these possibilities, and others, are still under investigation). The major unknown about the mechanism of oral treatment–induced desensitization or tolerance is whether ongoing exposure to the protein in the food is necessary to sustain long-term beneficial effects of the treatment.

OVERALL CONCLUSIONS

Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food. Various types of food allergies, such as immediate gastrointestinal hypersensitivity or eosinophilic gastroenteritis, occur and they can be classified as IgE-mediated and non-IgE-mediated food allergies. Many of them present common respiratory, gastrointestinal, and cutaneous signs and symptoms.

The definition and diagnosis of an allergy is rendered even more complicated because other gastrointestinal conditions, such as a food intolerance, can easily be misinterpreted as a food allergy. Given this diversity in signs and symptoms and underlying mechanisms, many misconceptions exist among the general public about what a food allergy is and how to identify one. More importantly, these misconceptions also are common among physicians, emergency care personnel, nurses, and others who are recognized as public health professionals. These misconceptions have tremendous implications for the public at large and specifically for allergic individuals and their families. For example, a diagnostic error can affect health outcomes, including psychological distress, or can lead to unnecessary management strategies.

Many fundamental mechanisms are now understood regarding how IgE-mediated food allergies develop and what is responsible for the signs and symptoms induced during allergic reactions to food. For example, it is well known that upon re-exposure following sensitization to an antigen, the antigen-induced aggregation of antigen-specific IgE binds to receptors on specialized cells (including mast cells in tissues and basophils in the blood). Such aggregation activates those specialized cells, releasing a variety of potent biological mediators that in turn result in the typical food allergy signs and symptoms. However, many questions are still being explored. A better understanding of the mechanistic processes underlying food allergy, and of the mechanisms that contribute to the various potential host responses to different forms of therapy for food allergy, will be invaluable in advancing the development of better prevention strategies, diagnostic methods, and treatments of food allergy.

RESEARCH NEEDS

Conducting research related to the mechanistic processes underlying food allergy is essential in making significant advances to develop better methods to prevent disease or reduce its severity; predict, diagnose, and monitor disease; and optimally manage and treat, and ultimately to cure, food allergy. These mechanistic processes include disease predispositions, origins and onset, normal and disordered oral tolerance to foods, factors that contribute to disease severity, and variation in individual responses to different forms of therapy.

One of the most prominent hypotheses for how food allergy develops—the dual-allergen hypothesis—proposes that environmental exposure to food allergens through the skin early in life can lead to allergy, while consumption of these foods during a developmentally appropriate period early in life results in tolerance. Under this hypothesis, children who avoid allergens in their diet but are still exposed to them in the environment might

be more likely to develop an allergy than those not exposed. Supporting this hypothesis are data suggesting that early dietary introduction of peanut products may confer protection against peanut allergy as well as data suggesting that loss of function of filaggrin, a protein important for epithelial structure, confers a risk for food sensitization. However, many questions remain about the mechanisms by which sensitization and tolerance occur and about which elements of the immune system represent the most important contributors to the severity of food allergy or the establishment of tolerance. For example, studies have shown that biochemical indicators of tolerance include a reduction in allergen-specific IgE production, decreased allergen-IgE-induced basophil activation, increased allergen-specific IgG4, and induction of Treg cells or anergic T cells. However, some of the data are conflicting and more studies are needed to better understand the role of these factors in food allergy

Another prevalent hypothesis is the microbial hypothesis, which states that the decrease in early childhood exposure to microbes may alter the development of early immunoregulatory responses, leading to the development of allergic disorders. For example, exposure to microbes during the perinatal period, may influence interactions between the developing microbiota and the immune system at the cellular and molecular levels and in turn affect health outcomes. Although the potential relationships between exposure to microbes early in life and the onset of food allergies have been explored, specific changes in the microbial profile of individuals, their particular interactions with the immune system, and how these interactions might be associated with food allergy have not been studied in depth.

To fill gaps in knowledge in this area, studies should be conducted to accomplish the following objectives:

- Elucidate the molecular and cellular mechanisms that account for the differences between innate tolerance versus food sensitization and between food sensitization versus food allergy.
- Identify the mechanisms, in patients with food allergies, for acquiring tolerance to the offending food allergen, without therapeutic intervention, as well as for responding to therapeutic interventions by developing transient desensitization versus sustained unresponsiveness versus true tolerance to the offending food allergens.
- Define how particular products and functions of mast cells, basophils, and other effector cells can contribute to the signs and symptoms of food allergic reactions, including anaphylaxis, and identify factors that may contribute to individual variation in the pathophysiological responses to such products.

- Study the role of immunoglobulins other than IgE, such as IgG4 or IgA, and of effector cells in addition to mast cells and basophils, in modulating (i.e., enhancing or reducing) food allergic responses.
- Identify and describe the roles of the skin and intestinal barriers in protecting individuals from developing food sensitization or a food allergy, and identify ways in which protective aspects of barrier function can be enhanced and factors that diminish barrier function be reduced.
- Examine the interactions between the microbiota and the host immune system that may favor or protect against the development of a food allergy, and define the extent to which the microbiota or its products can be manipulated to enhance resistance to the development of food allergy.

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3

Prevalence

Overall, food allergy has been estimated to cost $24.8 billion annually in the United States, including direct medical costs and costs borne by the family (Gupta et al., 2013a). To determine more accurate estimates of cost and to prioritize efforts, accurate prevalence[1] data are needed. Prevalence data also are important in helping to identify relationships between risk determinants and food allergies in specific populations. Various surveys of pediatricians and family practitioners, school teachers, school nurses, and the general public generally agree that the prevalence of food allergy in children has been increasing over the past two decades. A Data Brief published by the Centers for Disease Control and Prevention (CDC) in 2013 (Jackson et al., 2013) based on the National Health Interview Survey supports this notion (see Figure 3-1), but the true prevalence of food allergy in the past, or even the present, is uncertain and difficult to ascertain.

The term "food allergy" is often misunderstood and misused by the public and also by health care providers and researchers (see "Food Allergy Misconceptions" in Chapter 2), leading to inflated figures of prevalence reported from population-based surveys, ranging from 10 percent to 30 percent depending on the rigor of the questionnaires used. Even the definition of "food allergy" is not uniform (see "Commonly Accepted Definitions" in Chapter 2).

Unfortunately, no simple laboratory tests can be used to diagnose food allergy, especially non-immunoglobulin E (IgE)-mediated allergic reac-

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[1] Prevalence is the proportion of a population who have a specific characteristic (e.g., illness) in a given time period.
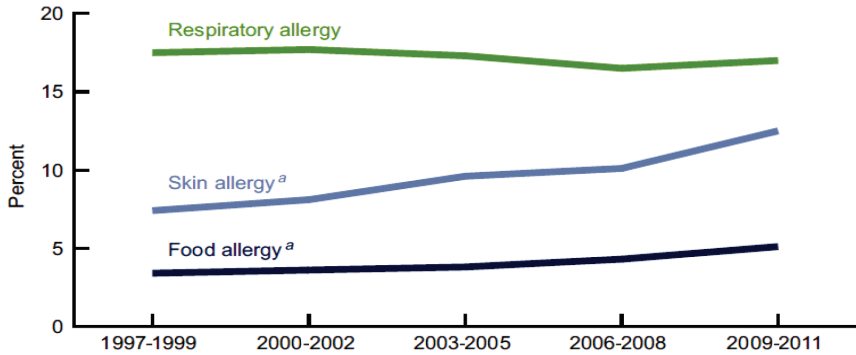
FIGURE 3-1 Increased prevalence of food and skin allergies in children ages 0 to 17 years, 1997-2011.
NOTES: Food allergy prevalence: Estimated based on an affirmative response to the National Health Interview Survey (NHIS) question: "During the past 12 months, has your child had any kind of food or digestive allergy?"
Respiratory allergy prevalence: Estimated based on affirmative responses to either of the two NHIS question(s): "During the past 12 months, has your child had hay fever?" and "During the past 12 months, has your child had any kind of respiratory allergy?"
Skin allergy prevalence: Estimated based on an affirmative response to the NHIS question: "During the past 12 months, has your child had eczema or any kind of skin allergy?"
[a] Significant increasing linear trend for food and skin allergy from 1997-1999 to 2009-1011.
SOURCES: CDC/NCHS, National Health Interview Survey, NCHS Data Brief, May 2013 (Jackson et al., 2013).

tions. Instead, physicians must rely on a combination of medical history, food-specific skin prick test (SPT) and/or food-specific serum IgE (sIgE) results, and/or oral food challenges[2] (OFCs) (preferably blinded) in order to accurately diagnose a food allergy (see Chapter 4). In a research setting, the gold standard to measure food allergy as an outcome is double-blind, placebo-controlled OFC (DBPCOFC). However, using such an approach in

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[2] There are three types of oral food challenges (OFCs) depending on the protocol. An open OFC is one where the food is in its natural form; a single-blind OFC is one where the food is masked from the patient's perspective so less patient bias occurs because of anxiety; a double-blind, placebo-controlled OFC involves masking the tested allergen and feeding it or indistinguishable placebo randomly without the patient or observer knowing if the allergen or placebo is being tested.

large population-based studies to ascertain prevalence is impractical, very labor-intense, and extremely expensive, and is therefore almost never done. The first real attempt to assess food allergy prevalence in the United States was conducted in 1987 (Bock, 1987). Although the study might be limited by selection bias and the small number of subjects, the use of OFC make this a landmark study.

This chapter addresses the difficulties inherent in attempting to ascertain the true prevalence of food allergy and the strength of the evidence based on the design of various trials. It summarizes current knowledge about IgE-mediated food allergy prevalence data in the United States and abroad. Given the complexity of diagnosing food allergy in population-based studies, both the prevalence of food sensitization (i.e., by SPT or serum IgE concentrations) and food allergy (i.e., the presence of clinical allergy as documented by an unequivocal clinical history and supportive laboratory studies or OFC) are presented. The prevalence of food allergies resulting from sensitization to the food and systemic reactions involving the skin, respiratory tract, gastrointestinal tract, and/or cardiovascular system will be considered. Prevalence data based on systematic reviews and meta-analyses from the United States and Europe are presented first, followed by data from individual studies in all countries, where available. It should be noted that the vast majority of data on the prevalence of food allergy has been ascertained in the pediatric population, often children in the first decade of life. Recommendations for data collection and analysis to improve the prevalence estimates for food allergy are included at the end of the chapter, along with research needs.

APPROACH TO LITERATURE REVIEW

The primary resources for this chapter on prevalence were derived from the 2010 National Institute of Allergy and Infectious Diseases/National Institutes of Health (NIAID/NIH)-supported *Guidelines for the Diagnosis and Management of Food Allergy in the United States* and its associated systematic reviews[3] (based on 51 publications) (Boyce et al., 2010; Chafen et al., 2010; Rona et al., 2007), and the 2014 European Academy of Allergy & Clinical Immunology's (EAACI's) *Food Allergy and Anaphylaxis Guidelines: Diagnosis and Management of Food Allergy* and its associated

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[3] According to the Cochrane Collaboration, "a systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review" (Moher et al., 2009). Statistical methods are often used to analyze and summarize the results of the studies included in the review.